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(54) **Title:** NOVEL COMPOSITIONS AND METHODS FOR CANCER

(57) **Abstract:** The present invention relates to novel sequences for use in diagnosis and treatment of caarcinomas, especially lymphoma carcinomas. In addition, the present invention describes the use of novel compositions for use in screening methods.

a) combining said CAP and a candidate bioactive agent; and

b) determining the effect of said candidate agent on the bioactivity of said CAP.

10. A method of evaluating the effect of a candidate carcinoma drug comprising:

a) administering said drug to a patient;

b) removing a cell sample from said patient; and

c) determining alterations in the expression or activation of a gene comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112.

11. A method of diagnosing carcinoma comprising:

a) determining the expression of one or more genes comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112, in a first tissue type of a first individual; and

b) comparing said expression of said gene(s) from a second normal tissue type from said first individual or a second unaffected individual;

wherein a difference in said expression indicates that the first individual has carcinoma.

12. A method for inhibiting the activity of a CA protein (CAP), wherein said CAP is encoded by a nucleic acid comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112, said method comprising binding an inhibitor to said CAP.

13. A method of treating carcinomas comprising administering to a patient an inhibitor of an CA protein (CAP), wherein said CAP is encoded by a nucleic acid comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112.

14. A method of neutralizing the effect of an CA protein (CAP), wherein said CAP is encoded by a nucleic acid comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112, comprising contacting an agent specific for said CAP protein with said CAP protein in an amount sufficient to effect neutralization.

15. A polypeptide which specifically binds to a protein encoded by a nucleic acid comprising a nucleic acid selected from the group consisting of the sequences outlined in Tables 1-112.

16. A polypeptide according to claim 15 comprising an antibody which specifically binds to a protein encoded by a nucleic acid comprising a nucleic acid sequence selected from the group consisting of the sequences outlined in Tables 1-112.

determined based on the number of homologous nucleosides in relation to the total number of nucleosides. Thus, for example, homology of sequences shorter than those of the sequences identified herein and as discussed below, will be determined using the number of nucleosides in the shorter sequence.

In one embodiment, the nucleic acid homology is determined through hybridization studies. Thus, for example, nucleic acids which hybridize under high stringency to the nucleic acids identified in the figures, or their complements, are considered CA sequences. High stringency conditions are known in the art; see for example Maniatis et al., Molecular Cloning: A Laboratory Manual, 2d Edition, 1989, and Short Protocols in Molecular Biology, ed. Ausubel, et al., both of which are hereby incorporated by reference. Stringent conditions are sequence-dependent and will be different in different circumstances. Longer sequences hybridize specifically at higher temperatures. An extensive guide to the hybridization of nucleic acids is found in Tijssen, Techniques in Biochemistry and Molecular Biology--Hybridization with Nucleic Acid Probes, "Overview of principles of hybridization and the strategy of nucleic acid assays" (1993). Generally, stringent conditions are selected to be about 5-10°C lower than the thermal melting point (Tm) for the specific sequence at a defined ionic strength pH. The Tm is the temperature (under defined ionic strength, pH and nucleic acid concentration) at which 50% of the probes complementary to the target hybridize to the target sequence at equilibrium (as the target sequences are present in excess, at Tm, 50% of the probes are occupied at equilibrium). Stringent conditions will be those in which the salt concentration is less than about 1.0 M sodium ion, typically about 0.01 to 1.0 M sodium ion concentration (or other salts) at pH 7.0 to 8.3 and the temperature is at least about 30°C for short probes (e.g. 10 to 50 nucleotides) and at least about 60°C for long probes (e.g. greater than 50 nucleotides). Stringent conditions may also be achieved with the addition of destabilizing agents such as formamide.
In another embodiment, less stringent hybridization conditions are used; for example, moderate or low stringency conditions may be used, as are known in the art; see Maniatis and Ausubel, supra, and Tijssen, supra.

In addition, the CA nucleic acid sequences of the invention are fragments of larger genes, i.e. they are nucleic acid segments. Alternatively, the CA nucleic acid sequences can serve as indicators of oncogene position, for example, the CA sequence may be an enhancer that activates a protooncogene. "Genes" in this context includes coding regions, non-coding regions, and mixtures of coding and non-coding regions. Accordingly, as will be appreciated by those in the art, using the sequences provided herein, additional sequences of the CA genes can be obtained, using techniques well known in the art for cloning either longer sequences or the full length sequences; see Maniatis et al., and Ausubel, et al., supra, hereby expressly incorporated by reference. In general, this is done using PCR, for example, kinetic

PCR.

Once the CA nucleic acid is identified, it can be cloned and, if necessary, its constituent parts recombined to form the entire CA nucleic acid. Once isolated from its natural source, e.g., contained within a plasmid or other vector or excised therefrom as a linear nucleic acid segment, the recombinant CA nucleic acid can be further used as a probe to identify and isolate other CA nucleic acids, for example additional coding regions. It can also be used as a "precursor" nucleic acid to make modified or variant CA nucleic acids and proteins.

The CA nucleic acids of the present invention are used in several ways. In a first embodiment, nucleic acid probes to the CA nucleic acids are made and attached to biochips to be used in screening and diagnostic methods, as outlined below, or for administration, for example for gene therapy and/or antisense applications. Alternatively, the CA nucleic acids that include coding regions of CA proteins can be put into expression vectors for the expression of CA proteins, again either for screening purposes or for administration to a patient.

In a preferred embodiment, nucleic acid probes to CA nucleic acids (both the nucleic acid sequences outlined in the figures and/or the complements thereof) are made. The nucleic acid probes attached to the biochip are designed to be substantially complementary to the CA nucleic acids, i.e. the target sequence (either the target sequence of the sample or to other probe sequences, for example in sandwich assays), such that hybridization of the target sequence and the probes of the present invention occurs. As outlined below, this complementarity need not be perfect; there may be any number of base pair mismatches which will interfere with hybridization between the target sequence and the single stranded nucleic acids of the present invention. However, if the number of mutations is so great that no hybridization can occur under even the least stringent of hybridization conditions, the sequence is not a complementary target sequence. Thus, by "substantially complementary" herein is meant that the probes are sufficiently complementary to the target sequences to hybridize under normal reaction conditions, particularly high stringency conditions, as outlined herein.

A nucleic acid probe is generally single stranded but can be partially single and partially double stranded. The strandedness of the probe is dictated by the structure, composition, and properties of the target sequence. In general, the nucleic acid probes range from about 8 to about 100 bases long, with from about 10 to about 80 bases being preferred, and from about 30 to about 50 bases being particularly preferred. That is, generally whole genes are not used. In some embodiments, much longer nucleic acids can be used, up to hundreds of bases.